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RESEARCH ARTICLE

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The effect of preoperative chemotherapy treatment in surgically treated intrahepatic cholangiocarcinoma patients—A multi-institutional analysis

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INTRODUCTION: While preoperative chemotherapy (pCT) is utilized in many intra-abdominal cancers, the use of pCT among patients with intrahepatic cholangiocarcinoma (ICC) remains ill defined. As such, the objective of the current study was to examine the impact of pCT among patients undergoing curative-intent resection for ICC.

METHODS: Patients who underwent hepatectomy for ICC were identified from a multi-institutional international cohort. The association between pCT with peri-operative and long-term clinical outcomes was assessed.

RESULTS: Of the 1 057 patients who were identified and met the inclusion criteria, 62 patients (5.9%) received pCT. These patients were noticed to have more advanced disease. Median OS (pCT:46.9 months vs no pCT:37.4 months; $P = 0.900$) and DFS (pCT: 34.1 months vs no pCT: 29.1 months; $P = 0.909$) were similar between the two groups. In a subgroup analysis of propensity-score matched patients, there was longer OS (pCT:46.9 months vs no pCT:29.4 months) and DFS (pCT:34.1 months vs no pCT:14.0 months); however this did not reach statistical significance (both $P > 0.05$).

CONCLUSION: In conclusion, pCT utilization among patients with ICC was higher among patients with more advanced disease. Short-term post-operative outcomes were not affected by pCT use and receipt of pCT resulted in equivalent OS and DFS following curative-intent resection.

KEYWORDS
intrahepatic cholangiocarcinoma, preoperative chemotherapy, prognostic factors, risk factors, survival

1 | INTRODUCTION

Intrahepatic cholangiocarcinoma (ICC) is the second most common primary liver malignancy, accounting for 3% of all cases of gastrointestinal cancer.[1,2] ICC makes up about 5-10% of all cholangiocarcinomas and originates from bile ducts within the liver parenchyma.[2,3] Histologically, the majority of advanced ICC tumors are adenocarcinoma, which are typically treated with a combination of cytotoxic nucleoside analogs and platins.[4,5] When feasible, complete surgical resection of ICC remains the only possible option for cure with an estimated median survival ranging from 27 to 36 months.[6–9] However, only a minority of patients with ICC present with surgically resectable

disease at the time of diagnosis. Even with complete surgical resection, recurrence can be as high as 50% within 24 months of surgical resection.[10] In addition, nearly one in five patients undergoing curative-intent resection are left with microscopic disease following surgery.[11] As such, there has been interest in using preoperative chemotherapy (pCT) to improve patient selection, increase the incidence of margin negative surgical resection and potentially improve disease-free (DFS) and overall survival (OS).

Preoperative chemotherapy is utilized in many intra-abdominal cancers to reduce local disease burden and the incidence of micrometastatic disease prior to surgical resection. In patients with perihilar cholangiocarcinoma (PHC), recent trials have shown that pCT may be effective in increasing DFS.[12] Furthermore, in patients with PHC, pCT can down-size locally advanced tumors in order to help facilitate surgical resection.[12] Despite this, the use of pCT among patients with ICC has not been well-studied.[5,12] As such, the objective of the current study was to determine the impact of pCT on OS and DFS in a large, multi-institutional international cohort of patients who underwent curative-intent resection for ICC. Furthermore, we sought to characterize current practice patterns regarding the use of pCT among patients undergoing curative-intent resection for ICC.

2 | METHODS

All patients undergoing curative-intent resection for ICC between January 1, 1990, and July 1, 2016 at one of 12 participating major hepatobiliary institutions in the United States, Asia, Oceania, and Europe were identified (Johns Hopkins University, Baltimore, Maryland; Emory University, Atlanta, Georgia; Stanford University Medical Center, Stanford, California; University of Virginia Health System, Charlottesville, Virginia; Fundeni Clinical Institute, Bucharest, Romania; Beaujon Hospital, Clichy, France; Curry Cabral Hospital, Lisbon, Portugal; Eastern Hepatobiliary Surgery Hospital, Shanghai, China; Ottowa General Hospital, Ottowa, Canada; Royal Prince Alfred Hospital, Sydney, Australia; San Raffaele Hospital, Milan, Italy; Erasmus University Medical Centre Rotterdam, Rotterdam, the Netherlands). Sociodemographic and clinicopathologic data were collected and include age, sex, and race, tumor size, AJCC stage, histologic grade, presence of nodal metastases, final resection margin and the presence of vascular and/or perineural invasion.

A minor hepatectomy was defined as a hepatic resection of less than 3 Couinaud segments. Suspected lymph node metastases on preoperative scans were considered suspicious preoperative lymph nodes, while only pathologically proven metastases were considered proven metastases. Patients with suspected lymph nodes preoperatively, and confirmed lymph node metastases during pathological examination of the resection specimen, were considered to have lymph node disease preoperatively and postoperatively, respectively. Patients with suspected lymph node disease preoperatively, but no evidence in the resection specimen, were considered to only have lymph node metastases preoperatively.

The American Joint Committee on Cancer (AJCC) 7th edition staging was used to stratify patients by extent of disease.[13] Margin status was categorized as R0 for a negative margin, R1 when the margin was microscopically positive and R2 when the margin was macroscopically positive. Only patients undergoing a curative intent surgery for histologically confirmed ICC were included in the final study population; patients who did not undergo resection were excluded. Patients who underwent transplantation were also excluded. The respective institutional review boards of each participating institution approved this study.

2.1 | Statistical analysis

Categorical variables were described as whole numbers and percentages while continuous variables were reported as medians with interquartile (IQR) range. Percentages for each variable were calculated based on available data, excluding missing values. Univariable comparison of categorical variables was performed using the Pearson chi-square test. Univariable comparison of continuous variables was performed using the Mann-Whitney U-test. The primary outcome of the study was 5-year OS. OS was calculated as the time from the date of surgery to the date of death or date of last available follow-up; OS was estimated using the Kaplan-Meier method. DFS was calculated from the date of surgery to the date of first-known radiographically or pathologically confirmed metastasis. Logistic regression analysis was conducted in order to determine factors associated with receipt of pCT in a multivariable model. Based on this regression model, a propensity score was calculated to determine the likelihood of receiving pCT. Patients were matched based on this propensity score and OS was compared between the groups. All analyses were performed using SPSS 22.0 (IBM, New York). All tests were 2-sided and $P < 0.05$ defined statistical significance.

3 | RESULTS

3.1 | Clinical and pathologic description of patient cohort receiving pCT

1 057 patients who underwent curative-intent resection for ICC and met the inclusion criteria were identified; 62 patients (5.9%) received pCT (Table 1). Among the patients who received pCT, 18 (29.0%) patients were treated with intra-arterial chemotherapy, while the remaining 44 patients (71.0%) were treated with systemic chemotherapy. Median patient age among patients who received pCT was 60 years (IQR 52, 69) and the majority of the patients were male ($n = 37$, 59.7%). Most patients had an ASA classification of II or III ($n = 51$, 92.7%).

Based on preoperative imaging and/or biopsy, over one-third of patients had suspected or proven lymph node metastases ($n = 21$, 39.6%). We observed that patients who received systemic chemotherapy more frequently had suspected or confirmed lymph node metastases ($n = 17$, 44.7%), compared to patients who received intra-arterial chemotherapy ($n = 4$, 26.7%). However, this difference did not reach statistical significance ($P = 0.226$). At the time of surgery, approximately one-half of patients underwent a major hepatectomy

TABLE 1 Characteristics of the preoperative chemotherapy group ($n = 62$)

Variable	*n* (%)/median (IQR)
Gender	
Male	37 (59.7)
Female	25 (40.3)
Age, years	60 (52-69)
Race	
Caucasian	49 (79.0)
African-American	8 (12.9)
Other	5 (8.0)
ASA	
I	3 (5.5)
II	24 (43.6)
III	27 (49.1)
IV	1 (1.8)
BMI	25.8 (23.5-29.0)
Period of treatment	
1990-2000	3 (5.3)
2001-2005	4 (7.0)
2006-2010	20 (35.1)
2011-2016	30 (52.6)
Preoperative chemotherapy type	
Intra-arterial therapy	18 (29.0)
Systemic therapy	44 (71.0)
Preoperative lymph node metastases	
No	32 (60.4)
Suspicious	12 (22.6)
Proven	9 (17.0)
Type of resection	
Minor hepatectomy (<3 segments)	6 (10.9)
Right hepatectomy	9 (16.4)
Left hepatectomy	8 (14.5)
Extended right hepatectomy	18 (32.7)
Extended left hepatectomy	11 (20.0)
Central hepatectomy	3 (5.5)
Lymphadenectomy	39 (70.9)
Lymph nodes harvested	3 (1-6)
Lymph node metastases	15 (24.2)
Extrahepatic metastases	8 (12.9)
Margin status	
R0	42 (73.7)
R1	14 (24.6)
R2	1 (1.8)

involving more than three Couinaud segments ($n = 29$, 52.7%). The majority of patients underwent a formal portal lymphadenectomy ($n = 39$, 70.9%), with a median of 3 lymph nodes (IQR: 1, 6) examined. On final pathology, the majority of patients had an R0 resection ($n = 42$, 73.7%). Lymph node metastasis was noted in 24.2% of patients ($n = 15$). Twelve patients (25.5%) who had lymph node metastases on the preoperative work-up did not have lymph node metastasis on final pathology.

3.2 | Receipt of preoperative chemotherapy

The majority of patients who received pCT ($n = 50$) were treated within the past 10 years, however the rate of pCT remained stable over the study period ($P = 0.632$). Several clinicopathologic features were associated with receipt of pCT (Table 2). Preoperatively, patients with suspected or biopsy-proven lymph nodes more likely received pCT (39.6% vs 18.5%, $P < 0.001$). Patients who received pCT were also more likely to have advanced disease compared with patients who did not receive pCT. Specifically, patients with microvascular invasion (pCT: $n = 25$, 48.1% vs no pCT: $n = 232$, 24.4%; $P < 0.001$) and perineural invasion (pCT: $n = 15$, 30.6% vs no pCT: $n = 137$, 15.6%; $P = 0.006$) more commonly received pCT. Furthermore, based on the AJCC 7th edition staging system, patients who received pCT more commonly had stage III or IV disease (pCT: $n = 16$, 55.2% vs no pCT: $n = 146$, 24.7; $P < 0.001$). The presence of extrahepatic disease was also associated with receipt of pCT (pCT: $n = 8$, 12.9% vs no pCT: $n = 32$, 3.2; $P < 0.001$). On final pathology, patients who received pCT also more often had microscopic R1 (pCT: $n = 14$, 24.6% vs no pCT: $n = 120$, 12.4%; or macroscopic R2 (pCT: $n = 1$, 1.8% vs no pCT: $n = 4$, 0.4%; $P = 0.010$) resections.

On multivariable analysis, after controlling for all measurable confounders, factors associated with receipt of pCT included major hepatic resection (OR: 3.88, 95%CI 1.43-10.49, $P = 0.008$) and the presence of microvascular invasion (OR: 2.93, 95%CI 1.43-6.02, $P = 0.003$).

3.3 | Perioperative morbidity

Overall morbidity among all patients who underwent resection for ICC was 40.2% ($n = 420$) with a higher incidence of complications occurring among patients who received pCT (pCT: $n = 36$, 59.0% vs no pCT: $n = 384$, 39.0%; $P = 0.002$); major morbidity, however, did not differ between the two groups ($P = 0.568$) (Table 3). Median length of stay (pCT: 9 days, IQR 6,15 vs no pCT: 12 days, IQR 7,17; $P = 0.080$) and perioperative mortality within 90 days of surgery (pCT: $n = 1$, 2.2% vs no pCT: $n = 35$, 3.9%; $P = 0.569$) also did not differ between the two groups. Readmission within 30 days from surgery, however, was more common among patients who received pCT (pCT: $n = 8$, 15.7% vs no pCT: $n = 39$, 4.8%; $P = 0.001$). Post-operatively, patients in the pCT group more often received adjuvant chemotherapy (50.8% vs 29.0%, $P = 0.001$).

3.4 | Impact of preoperative chemotherapy on overall and disease-free survival

At a median follow-up of 27.6 months, mortality occurred in 522 (49.7%) patients. Median OS among the entire cohort was 37.4 months (95%CI 32.5-42.3 months) with 1-, 3-, and 5-year OS being 78.9%, 51.4%, and 39.2%, respectively. Stratified by receipt of pCT, median OS was similar between the two groups (pCT: 46.9 months,

TABLE 2 Comparison of disease characteristics across treatment groups

Variable	No Preoperative Chemotherapy (*n* = 995)	Preoperative Chemotherapy (*n* = 62)	*P*-value
Preoperative lymph node metastases			<0.001
No	699 (81.2)	32 (60.4)	
Suspicious	121 (14.1)	12 (22.6)	
Proven	38 (4.4)	9 (17.0)	
Type of resection			<0.001
Minor hepatectomy (<3 segments)	413 (42.6)	6 (10.9)	
Right hepatectomy	158 (16.3)	9 (16.4)	
Left hepatectomy	185 (19.1)	8 (14.5)	
Extended right hepatectomy	110 (11.4)	18 (32.7)	
Extended left hepatectomy	85 (8.8)	11 (20.0)	
Central hepatectomy	18 (1.9)	3 (5.5)	
Number of tumors	1 (1-1)	1 (1-1)	0.207
Tumor size (cm)	6.0 (4.2-8.8)	7.1 (5.0-10.2)	0.069
Major vascular invasion	95 (9.8)	5 (8.9)	0.832
Microvascular invasion	232 (24.4)	25 (48.1)	< 0.001
Perineural invasion	137 (15.6)	15 (30.6)	0.006
Invasion of adjacent organs	72 (7.4)	5 (8.9)	0.676
Satellite lesions	216 (22.2)	17 (29.8)	0.181
Intrahepatic metastases	69 (7.1)	6 (10.7)	0.308
Lymphadenectomy	424 (43.7)	39 (70.9)	< 0.001
Lymph nodes harvested	2 (0-5)	3 (1-6)	0.074
Lymph node metastases	169 (17.0)	15 (24.2)	0.146
Extrahepatic metastases	32 (3.2)	8 (12.9)	< 0.001
Margin status			0.010
R0	840 (87.1)	42 (73.7)	
R1	120 (12.4)	14 (24.6)	
R2	4 (0.4)	1 (1.8)	
AJCC stage			< 0.001
I	282 (48.0)	7 (24.1)	
II	160 (27.2)	6 (20.7)	
III	22 (3.7)	6 (20.7)	
IVA	112 (19.0)	8 (27.6)	
IVB	12 (2.0)	2 (6.9)	

95%CI 28.5-65.2 months vs no pCT: 37.4 months, 95%CI 32.3-42.5 months; $P = 0.900$; Fig. 1). Disease recurrence occurred in 454 (43.0%) patients. Median DFS among the entire cohort was 29.6 months (95% CI 17.2-42.0 months) with 1-, 3-, and 5-year DFS being 64.7%, 46.6%, and 44.4%, respectively. Stratified by receipt of pCT, median DFS was also similar between the two groups (pCT: 34.1 months, 95%CI 2.5-65.7 months vs no pCT: 29.1 months, 95%CI 16.0-42.2 months; $P = 0.909$; Fig. 2).

In a subgroup analysis of propensity-score matched patients based on the factors associated with receipt of pCT ($n = 100$), there was longer OS in the pCT group (pCT: 46.9 months, 95%CI 24.3-69.4 months vs no pCT: 29.4 months, 95%CI 14.5-44.4 months), however this did not reach statistical significance ($P = 0.136$; Fig. 3). Similarly, there was suggestion of an improved DFS in the pCT group (pCT: 34.1 months, 95%CI 0-70.2 months vs no pCT:14.0 months, 95%CI 7.0-20.9 months; $P = 0.551$).

4 | DISCUSSION

Preoperative therapy is used in several intra-abdominal cancers to reduce local and micrometastatic tumor burden prior to complete surgical resection. Some benefits of pCT include the potential to down-size tumors to increase resectability rates among patients who are initially deemed unresectable. Furthermore, pCT can potentially improve completeness of surgical resection, as well as help select patients with a better tumor biology, thereby improving OS and DFS. In the current study, we examined a large, multi-institutional

TABLE 3 Comparison of postoperative course and follow-up across treatment groups

Variable	No preoperative chemotherapy (n = 995)	Preoperative chemotherapy (n = 62)	P-value
Complication	384 (39.0)	36 (59.0)	0.002
Clavien dindo grade			0.568
I-II	239 (58.0)	23 (53.5)	
III-V	173 (42.0)	20 (46.5)	
Length of stay (days)	12 (7-17)	9 (6-15)	0.080
Readmission within 30 days	39 (4.8)	8 (15.7)	0.001
Postoperative mortality	35 (3.9)	1 (2.2)	0.569
Adjuvant therapy			
Adjuvant intra-arterial therapy	102 (14.1)	7 (14.6)	0.921
Adjuvant chemotherapy	270 (29.0)	30 (50.8)	0.001
Adjuvant radiotherapy	56 (6.4)	6 (10.7)	0.203

international cohort of patients receiving pCT for ICC. As the use of pCT among patients with ICC has not been well-studied, this represents to our knowledge the largest study to date analyzing the impact of pCT among patients undergoing curative-intent resection for ICC. We noted that patients with more advanced disease were more likely to receive pCT. Of note, the use of pCT did result in higher overall but not major perioperative morbidity. Furthermore, in the propensity score-matched cohort, there was a suggestion that pCT improved OS and DFS, however these differences did not reach statistical significance perhaps due to a small sample size.

The use of pCT has not been examined among patients with ICC in any prospective clinical trial to date. Likely due to the overall low incidence of ICC, patients with ICC are often grouped in clinical trials with other patients with biliary tract cancers. As such, the benefit of pCT in patients with ICC is ill-defined and not commonly utilized.[2,14–16] In fact, in the current multi-institutional international cohort, the overall utilization of pCT was only 5.9%. This is likely due to the fact that analyses from available studies have been unable to show a reproducible benefit with the use of pCT among patients with ICC.[2,16] Among patients with pancreatic adenocarcinoma, however, pCT has been used in patients with locally advanced tumors to define the tumor biology.[17] In the current cohort, patients with more advanced disease were more likely to receive pCT – suggesting that physicians were using pCT, in part, to help define the natural history of the disease. Specifically, patients with more preoperative suspected or biopsy-proven lymph node metastasis, as well as those patients with worse pathological tumor features more commonly received pCT. Unfortunately, as the current cohort only included patients undergoing curative-intent hepatic resection for ICC, we were unable to determine the rate of resectability among patients with locally advanced disease. Of note, on final pathology, the use of pCT did not improve complete R0 resection rates. This is likely multifactorial, but largely be due to the selection of pCT use for patients with tumors characterized by worse pathological features.

Patients who received pCT had increased minor, but not major perioperative morbidity or mortality rates versus patients who did not receive pCT. This is similar to previously published data regarding the safety of pCT among patients undergoing resection for intra-abdominal cancer.[18,19] Despite having more advanced disease and undergoing larger hepatic resections, patients who received pCT had equivalent peri-operative mortality and LOS. While long-term OS and DFS were comparable among patients who did and did not receive pCT, propensity score-matched analysis suggested a possible benefit of pCT regarding both OS and DFS—although the association did not

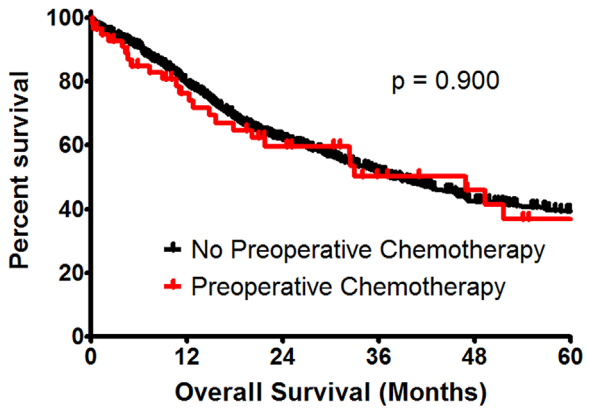

FIGURE 1 Overall survival stratified by preoperative chemotherapy (P = 0.900)

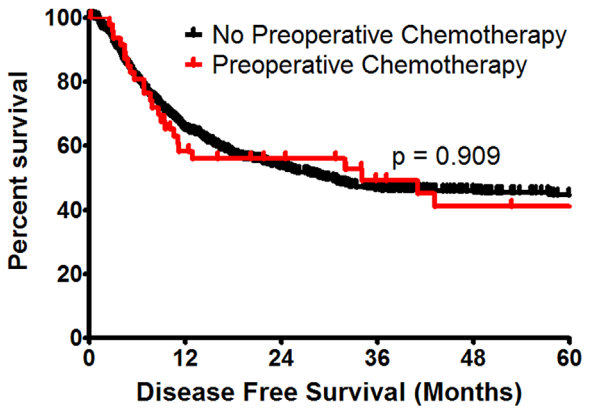

FIGURE 2 Disease free survival stratified by preoperative chemotherapy (P = 0.909)

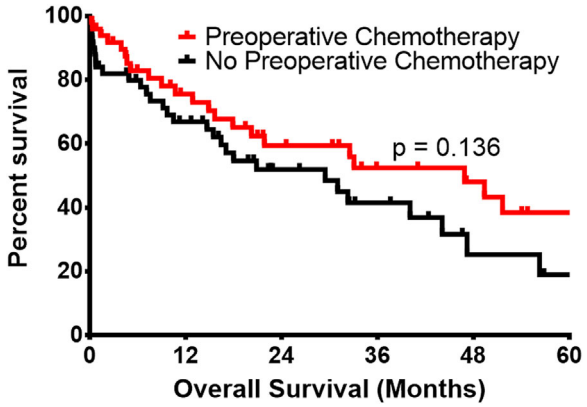

FIGURE 3 Overall survival propensity score-matched patients for resection and microvascular invasion ($P = 0.136$)

reach statistical significance. While it is difficult to know, the lack of significance, despite the considerable differences in the point estimates, was likely due to a type II statistical error given the very low utilization of pCT in the current cohort. Nelson et al had reported that the use of pCT combined with radiation therapy improved survival outcomes among patients with extrahepatic cholangiogcarcinoma.[20] In a different study, Tamandl et al reported on 10 patients with ICC who were treated with pCT and noted no survival benefit.[21] While the current study was one of the largest series to examine ICC patients to receive pCT ($n = 62$), we similarly failed to find an effect of pCT on long-term outcomes. As noted, however, the sample size was still relatively small and therefore future prospective studies are needed.

In this study, we included 18 patients who received preoperative intra-arterial chemotherapy, as opposed to the 44 patients who received systemic chemotherapy. Intra-arterial therapy consists of the delivery of high doses of chemotherapy directly to the arterial circulation.[9] This results in high first pass extraction rates and minimizes systemic toxicity, as tumors derive most of their supply from the arterial circulation.[9,22] The effects of intra-arterial therapy have been described in two clinical trials and a retrospective analysis, which showed promising results in patients with liver-confined disease in a palliative setting.[9,23,24] In our cohort, the lower percentage of patients with preoperatively confirmed lymph node metastases in the intra-arterial chemotherapy group (26.7% vs 44.7%), suggests that intra-arterial therapy was most often used preoperatively in patients with suspected borderline resectable disease, as opposed to patients with suspected micrometastatic disease. Although our finding is in line with current literature on patients with irresectable disease, future studies are needed to confirm the validity of this approach prior to a curative resection.

Results of the current study should be interpreted in the context of several limitations. As noted, the number of patients treated with pCT was small as the overall utilization was only 5.9%. Therefore, the lack of statistical significance was likely related to a type II error. Additionally, inherent to all retrospective analyses, there may have been a selection bias regarding the diagnosis and treatment of patients. The inclusion of multiple centers also did not allow for the standardization of operative approach or protocols related to the use of pCT or adjuvant chemotherapy. The multi-center nature of the study adds to the generalizability of the study, allowing the finding to be applied across a wide range of patient populations.

5 | CONCLUSIONS

In conclusion, pCT utilization among patients with ICC is higher among patients with more advanced disease. In this large, multi-institutional cohort, the use of pCT did not impact short-term peri-operative outcomes such as morbidity or LOS. While OS and DFS following resection were not significantly different across treatment groups, propensity matching suggested possible improved outcomes in patients treated with pCT. Further prospective trials are needed, however, to better define the role of pCT and to identify the subset of patients who might yield the most clinical benefit from the use of pCT.

POTENTIAL CONFLICTS OF INTEREST

Nothing to disclose.

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